Interrupting Anticoagulation in Patients With Nonvalvular Atrial Fibrillation

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ABSTRACT

Three target-specific oral anticoagulants (TSOACs)—dabigatran, rivaroxaban, and apixaban—have been approved by the FDA to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation; however, no agents are currently approved to reverse the anticoagulant effects of these TSOACs in cases of active bleeding. This review discusses the benefits and risks of these TSOACs from a clinician’s perspective, with a focus on the interruption of treatment for either elective or emergent surgery, monitoring, and reversal of anticoagulation. Available coagulation assays are not ideal for monitoring the effects of TSOACs and do not provide reliable quantitative measurement of their anticoagulant effects. When necessary, activated partial thromboplastin time (aPTT) may provide qualitative information on dabigatran, and prothrombin time (PT) may provide qualitative assessment of the presence of the factor Xa inhibitors, rivaroxaban and apixaban. Current recommendations for reversal of TSOACs are based largely on limited and sometimes conflicting data from in vitro or in vivo animal models, and clinical experience with these recommendations is also limited. Methods that have been investigated for effectiveness for reversal of the pharmacodynamic effects of the TSOACs include dialysis, activated charcoal, prothrombin complex concentrate (PCC), and recombinant activated factor VII. It is important to note that even within a class of anticoagulant drugs, compounds respond differently to reversal agents; therefore, recommendations for one agent should not be extrapolated to another, even if they are from the same therapeutic class. New antidotes are being explored, including a mouse monoclonal antibody to dabigatran; andexanet alfa, a potential universal factor Xa inhibitor reversal agent; and a synthetic small molecule (PER977) that may be effective for the reversal of factor Xa inhibitors and direct thrombin inhibitors. Given the short half-lives of TSOACs, watchful waiting, rather than reversal, may be the best approach in some circumstances.

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia, and its prevalence is growing worldwide.1,2 Nonvalvular atrial fibrillation (NVAF) is associated with an increased risk of stroke; long-term anticoagulation is recommended for the prevention of stroke in most patients. Warfarin (Coumadin, Bristol-Myers Squibb) and other vitamin K antagonists (VKAs) are highly effective oral anticoagulants for reducing the risk of stroke in patients with NVAF, but their use is limited by a narrow therapeutic range; drug and food interactions; the requirement for routine monitoring; and, as with all anticoagulant therapies, an increased risk of bleeding.3 Recently, target-specific oral anticoagulants (TSOACs), also known as novel oral anticoagulants (NOACs), including dabigatran etexilate (Pradaxa, Boehringer Ingelheim), apixaban (Eliquis, Bristol-Myers Squibb/Pfizer), and rivaroxaban (Xarelto, Janssen Pharmaceuticals), have been developed as alternatives.4-7 As the TSOACs are integrated into clinical practice, clinicians are relieved of some of the past challenges related to warfarin treatment but are also presented with new questions, particularly related to the interruption of anticoagulation. The issues of how and when to interrupt anticoagulation emergently in the setting of bleeding or electively to minimize bleeding risk can be frustrating for clinicians faced with limited guidance on these issues. The aim of this review is to provide clinicians with a practical discussion of how to manage interruptions in anticoagulation and the associated clinical issues of monitoring and reversal of anticoagulation.

EMERGENCE OF THE TARGET-SPECIFIC ORAL ANTICOAGULANTS

In 2010, dabigatran etexilate (150 mg), a direct thrombin inhibitor, became the first TSOAC to be approved by the Food and Drug Administration (FDA) to reduce the risk of stroke or systemic embolism in patients with NVAF.8 Rivaroxaban and apixaban, both factor Xa (FXa) inhibitors, were approved for the same indication in 2011 and 2012, respectively.9,10 Both rivaroxaban and apixaban are indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery,5,10 and dabigatran, rivaroxaban and apixaban are also indicated for the treatment of DVT and PE, as well as reduction in the risk of their recurrence.5,9,11 Three additional FXa inhibitors, edoxaban, betrixaban, and letaxaban, are in various stages of development.12-16 Approvals for the use of dabigatran, rivaroxaban, and edoxaban, and etoxaban to reduce the risk of stroke or systemic embolism in patients with NVAF and other indications vary by country.17-20

Although several medical societies, including the American College of Cardiology, American Heart Association (AHA), Heart Rhythm Society, American College of Chest Physicians, European Society of Cardiology, and American Academy of Neurology, have provided guidance on the use of TSOACs in the form of recent guideline updates,21-24 the incorporation of TSOACs into clinical practice introduces several important clinical issues for which evidence-based guidelines are not yet available: monitoring of anticoagulation, interruption of therapy, and reversal of anticoagulation, all key clinical concerns.

Disclosures: Dr. Yates is an investigator for the RE-LY (Boehringer Ingelheim), ROCKET-AF (Bayer, Johnson & Johnson), and ARISTOLE (Bristol-Myers Squibb/Pfizer) clinical trials. In addition, he has performed clinical trials in association with approximately 30 other pharmaceutical and health care improvement organizations, including Janssen Pharmaceuticals and Novo Nordisk. Bristol-Myers Squibb and Pfizer funded professional medical writing and editorial assistance for this article.

Dr. Yates is Founder and President of the Center for Executive Medicine in Plano, Texas.
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MONITORING ANTICOAGULATION

Of great concern to clinicians is how to know when it is safe to proceed with surgery in anticoagulated patients, especially in those who are elderly, have low body weight, or have reduced renal function. The short half-lives of the TSOACs allow clinicians to estimate when their anticoagulant effects will be reduced; however, it would be useful to have effective monitoring techniques that define the absence of the anticoagulant effect for each agent so that clinicians can determine when it is safe to proceed with surgery. Due to their short half-lives, it is important to take the timing of the last dose into account when interpreting test results for the anticoagulant effect of the TSOACs.25 In addition, when bleeding is suspected, physicians should consider measuring creatinine clearance to rule out functional overdose resulting from a change in kidney function. A complete blood count with platelets will also provide useful information when investigating a possible bleed.

In addition to international normalized ratio (INR), other assays have been used to evaluate the anticoagulant effects of the TSOACs, with varying degrees of success. Assays that may be considered to identify the absence of an anticoagulant effect for one or more of the TSOACs (dabigatran, rivaroxaban, or apixaban) include the prothrombin time (PT), thrombin time (TT), activated partial thromboplastin time (aPTT), ecarin clotting time (ECT), anti-FXa, prothrombinase-induced clotting time, and modified prothrombin time assays (Table 1). With the exception of the PT assay (for assessing the anticoagulant effect of warfarin), these tests are not useful for routine monitoring or for determining whether anticoagulation is appropriate or therapeutic.

Validated quantitative assays for monitoring the anticoagulant effects of TSOACs are not yet available. Nevertheless, certain available assays may provide helpful qualitative information when it is necessary to assess the anticoagulant effects of each of the TSOACs. For instance, aPTT may provide qualitative information on the presence of dabigatran. An aPTT level greater than two times the upper limit of normal 12 to 24 hours postdose (time of trough dabigatran concentration) may indicate a higher risk of bleeding.25 PT may provide a qualitative assessment of the presence of the FXa inhibitors apixaban and rivaroxaban. As with aPTT for dabigatran, however, results should not be considered quantitative and should be interpreted with caution.25 Correspondingly, the apixaban prescribing information warns that: “Changes observed in these clotting tests [PT, INR, and aPTT] at the expected therapeutic dose, however, are small, subject to a high degree of variability, and not useful in monitoring the anticoagulation effect of apixaban.”11

INTERRUPTION OF ANTICOAGULATION

When considering any interruption of treatment, the risk of bleeding should be weighed against the risk of stroke or thromboembolism. The FDA has issued boxed warnings for all three TSOACs stating that treatment discontinuation without adequate continuous anticoagulation places patients at an increased risk of thrombotic events.8,9,11 To reduce this risk, clinicians should consider administration of another anticoagulant if treatment is discontinued for reasons other than pathological bleeding. When switching between TSOACs, it is recommended to discontinue one anticoagulant and begin the other at the next scheduled dose.

Emergent Versus Elective Interruption

Occasionally, circumstances require interruption of ongoing anticoagulation, either emergently or electively. Emergent interruption is nearly always associated with an acute, life-threatening event, such as serious bleeding into critical organs, potential overdose, or the need for emergency surgery or invasive diagnostic procedures such as lumbar puncture. Elective interruption may be necessary during an elective invasive procedure (e.g., cutaneous, ophthalmic, or dental procedures) and some nonsurgical procedures (e.g., colonoscopy). Best practices for perioperative use of TSOACs are still emerging; however, guidelines are available for perioperative use of warfarin.26 For elective interventions associated with a low risk of bleeding (e.g., dental cleaning or extractions, skin biopsy, cataract surgery), anticoagulant drugs may not have to be interrupted. Anticoagulants do need to be stopped prior to procedures associated with an intermediate risk of bleeding (e.g., polyp resection at time of colonoscopy or laparoscopic cholecystectomy) or a high risk of bleeding (e.g., joint arthroplasty, urological surgery, neurosurgery, or abdominal or pelvic surgery).

Table 1 Anticoagulant Half-Lives and Recommendations for Assays To Define the Absence of Each Agent’s Anticoagulant Effect

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>FDA-Approved Dosages</th>
<th>Half-Life</th>
<th>Monitoring Assay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>Target INR 2–3</td>
<td>40 hours</td>
<td>PT ≥ 3</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>150 mg b.i.d. (CrCl &gt; 30 mL/min) 75 mg b.i.d. (CrCl 15–30 mL/min)</td>
<td>14–17 hours</td>
<td>ECT,* aPTT, TT, Hematoclot*81–84</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>20 mg q.d. (CrCl &gt; 50 mL/min) 15 mg q.d. (CrCl 15–50 mL/min)</td>
<td>5–9 hours</td>
<td>Anti-FXa, PT, PICT*85,86</td>
</tr>
<tr>
<td>Apixaban</td>
<td>5 mg b.i.d. 2.5 mg b.i.d. in patients with at least two of these characteristics: age ≥ 80 years, body weight ≤ 60 kg, serum creatinine ≥ 1.5 mg/dL</td>
<td>9–14 hours</td>
<td>Anti-FXa, mPT,* HepTest*45,87</td>
</tr>
</tbody>
</table>

* Not widely available

aPTT = activated partial thromboplastin time; anti-FXa = anti-factor Xa; b.i.d. = twice daily; CrCl = creatinine clearance; ECT = ecarin clotting time; INR = international normalized ratio; mPT = modified prothrombin time; PICT = prothrombinase-induced clotting time; PT = prothrombin time; q.d. = daily; TT = thrombin time
embolism, however, bridging anticoagulation with heparin should be considered. Warfarin should then be resumed at the usual maintenance dose (without a loading dose) on the evening of or the morning after the procedure, assuming there is adequate hemostasis. If an invasive procedure is required when the INR is still elevated (more than 1.5), a low dose of oral vitamin K (1 mg or 2 mg) may be considered to normalize the INR.

**Interruption of Dabigatran Anticoagulation**

Dabigatran should be discontinued one to two days before an invasive procedure in patients with creatinine clearance of at least 50 mL/min and three to five days preoperatively in patients with a creatinine clearance of less than 50 mL/min. Discontinuation of dabigatran for a longer time may be considered for patients undergoing major surgery, spinal puncture, or placement of a spinal or epidural catheter or port, or in patients for whom complete hemostasis may be required. Normalization of the TT assay suggests the absence of dabigatran’s anticoagulant effect. Similarly, normalization of the aPTT assay indicates the absence of dabigatran’s anticoagulant effect. During the RE-LY trial, anticoagulation with dabigatran was discontinued at least 24 hours prior to elective surgery, or longer for patients with high risk of bleeding or poor kidney function, and resumed as soon as clinically feasible post-procedurally. Use of this strategy for patients undergoing surgery in RE-LY resulted in patients receiving the last dose of dabigatran 49 hours (interquartile range [IR], 35–85 hours) before a procedure in comparison with 114 hours (IR, 87–144 hours) for patients receiving warfarin (P < 0.001), and patients treated with dabigatran had rates of bleeding similar to patients treated with warfarin (3.8%, 5.1%, and 4.6% for dabigatran 110 mg, dabigatran 150 mg, and warfarin, respectively).

**Interruption of Rivaroxaban Anticoagulation**

Rivaroxaban should be discontinued at least 24 hours before an invasive procedure to reduce the risk of bleeding. The increased risk of bleeding should be weighed against the urgency of the intervention in deciding whether to delay a procedure for 24 hours after discontinuing rivaroxaban. Rivaroxaban should be restarted after the intervention as soon as adequate hemostasis has been established. If oral medication cannot be taken, a parenteraly administered anticoagulant should be considered. Normalization of the PT, aPTT, or anti-FXa assay might suggest absence of rivaroxaban’s anticoagulant effect. In 90% of temporary interruptions due to a procedure in ROCKET-AF, the drug was stopped three days or more before the procedure, and participants with interruptions for invasive procedures had rates of major bleeding and nonmajor clinically relevant bleeding of approximately 1% and 3% per 30 days, respectively, which were similar between treatment groups.

**Interruption of Apixaban Anticoagulation**

In patients undergoing invasive procedures with a low risk of bleeding or where the bleeding would be in a noncritical location and easily controlled, apixaban should be discontinued 24 hours prior to the procedure. For invasive procedures associated with a moderate or high risk of clinically significant bleeding, apixaban should be discontinued 48 hours prior to the procedure. Normalization of the anti-FXa may suggest the absence of apixaban’s anticoagulant effect; however, PT and aPTT are not reliable indicators of apixaban pharmacodynamics, and normalization of these values may not suggest an absence of anticoagulant effects of apixaban. During ARISTOTLE, the majority of procedures were nonmajor (96%) and nonemergent (97%). The study drug was stopped in 64% of procedures, and the median time of study drug interruption was four days before the procedure for both apixaban- and warfarin-treated patients. The rates of clinical events were found to be comparable between the warfarin and apixaban groups in a post-hoc analysis in the first 30 days post-procedure, both overall and for emergent procedures.

**REVERSING ANTICOAGULATION**

Compared with warfarin, the TSOACs have shorter half-lives (Table 1). Therefore, there may be less need for pharmacological interventions to reverse their anticoagulant effects. However, rapid reversal of anticoagulation may be needed in cases of bleeding or when emergent surgery is necessary. While some options are available for reversal of warfarin treatment, there are currently no interventions that have demonstrated a benefit in bleeding patients treated with TSOACs. However, data on possible reversal strategies are emerging from in vivo and in vitro animal models, as well as from some limited clinical experience. The results of the different reversal strategies tested to date are summarized in Table 2. It should be noted that the FDA has not approved any specific reversal agent for use with any of the TSOACs.

**Table 2 Recommendations for Reversal Strategies**

<table>
<thead>
<tr>
<th>Time Frame</th>
<th>Strategies</th>
<th>Effective*</th>
<th>Consider</th>
<th>Not Effective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>Vitamin K†, FFP, aPCC</td>
<td>24 hours</td>
<td>3 hours</td>
<td>1 hour</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Dialysis*, aPCC (FEIBA)*, PER977 (when available)</td>
<td>48 hours</td>
<td>24 hours</td>
<td>12 hours</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>PCC (Cofact)<em>, aPCC (FEIBA)</em>, Andexanet alfa (when available)</td>
<td>48 hours</td>
<td>24 hours</td>
<td>12 hours</td>
</tr>
<tr>
<td>Apixaban</td>
<td>rFVIIa*, aPCC (FEIBA)*, Andexanet alfa (when available)</td>
<td>48 hours</td>
<td>24 hours</td>
<td>12 hours</td>
</tr>
</tbody>
</table>

* Data for reversal of dabigatran, rivaroxaban, and apixaban come primarily from animal studies.
† As noted in the prescribing information
aPCC = activated prothrombin complex concentrate; FEIBA = factor VIII inhibitor bypass activity; FFP = fresh frozen plasma; PCC = prothrombin complex concentrate; rFVIIa = recombinant activated factor VIIa
The Limitations of Anticoagulant Reversal

Despite concerns about a lack of reversal agents for TSOACs, the reversal agents available for warfarin do not always facilitate better clinical outcomes. For example, in a secondary analysis of RE-LY, mortality rates and outcomes were similar in 154 cases of intracranial hemorrhage (ICH) in the dabigatran and VKA arms. Although details regarding reversal were not elaborated upon, these results suggest that having a reversal agent available for VKA had little effect on patient outcomes. Additionally, in a Canadian multicenter registry, prothrombin complex concentrate (PCC) rapidly corrected INR in most patients with anticoagulant-associated ICH, yet mortality and morbidity rates remained high. Importantly, all three TSOACs have been shown to markedly reduce the rates of ICH compared with warfarin.

As noted, current recommendations for the reversal of TSOACs are mostly based on limited data from in vitro or in vivo animal models, and clinical experience with these recommendations is limited. There are inherent differences in the pharmacokinetics and pharmacodynamics of each of the TSOACs; therefore, recommendations for one agent should not be extrapolated to the others, even if the products are from the same therapeutic class (e.g., rivaroxaban and apixaban).

Reversal of Warfarin Anticoagulation

Vitamin K. Parenteral or oral vitamin K has been shown to counteract the effect of warfarin, although this effect is not immediate, even with intravenous administration. In patients with elevated INR levels, the time to effect is approximately 24 hours after oral administration and four to 12 hours after intravenous administration, with similar effectiveness seen for both routes at 24 hours. FFP has been used successfully to reverse the anticoagulant effects of warfarin; however, the efficacy of FFP is limited by the risk of allergic and infectious transfusion reactions, processing time, and the volume required for correction.

Fresh frozen plasma (FFP). FFP has been suggested for reversing the anticoagulant effect of dabigatran but has shown limited effectiveness in a murine ICH model for reduction of intracerebral hematoma; it is not recommended for this use.

Dialysis. Dabigatran is dialyzable due to its relatively low plasma protein binding (approximately 60% of the drug over two to three hours); however, data supporting this approach are limited. A 2012 case report described the use of dialysis to remove dabigatran in an elderly man with normal kidney function who presented with severe ICH. The patient’s dabigatran level decreased from 312 ng/mL at the time of admission (10 hours before the start of dialysis), to 49 ng/mL after one hour of dialysis, and 29 ng/mL after three hours of dialysis. Notably, the patient experienced a rebound in dabigatran plasma concentration to 43 ng/mL two hours after dialysis, most likely due to the large volume of distribution of dabigatran.

In contrast, rivaroxaban and apixaban are highly protein-bound. A high proportion of rivaroxaban (92%–95%) is bound to protein in the plasma, making dialysis an unlikely option for this TSOAC. A recent study showed that hemodialysis may be useful for apixaban elimination in patients with end-stage renal disease; however, because of a high degree of protein binding (92%–94%), hemodialysis is also not recommended for the reversal of the anticoagulant effect of apixaban.

Activated charcoal. Activated charcoal may be used to reduce absorption of TSOACs when administered shortly after dosing. It has been recommended for removal of dabigatran and rivaroxaban if administered within two and eight hours of ingestion, respectively; however, no in vivo analyses have been conducted to test this hypothesis. A study assessing the effect of activated charcoal on the pharmacokinetics of orally administered apixaban in 18 healthy subjects found that activated charcoal given at two and six hours postdose substantially reduced apixaban exposure, with the area under plasma concentration–time curve from time zero to infinity (AUC\textsubscript{INF}) reduced by 50% and 28%, respectively. Thus, administration of activated charcoal up to six hours after apixaban ingestion may be useful in the management of apixaban overdose or accidental ingestion.


**Recombinant activated factor VIIa.** The use of rFVIIa to reverse the anticoagulant effects of dabigatran has been tested in a murine ICH model; however, rFVIIa (8 mg/kg) did not inhibit intracerebral hematoma expansion.60 Despite the negative results shown in the murine ICH model, a case report has been published of a patient enrolled in RE-LY (dabigatran 150 mg twice a day) for whom the administration of rFVIIa reduced the rate of bleeding from more than 1,500 mL/h to 800 mL/h.45 This patient, a 79-year-old 80-kg man with non–insulin-dependent diabetes and chronic renal insufficiency (estimated creatinine clearance, 36 mL/min) underwent cardiac surgery two days after dabigatran discontinuation, resulting in severe postoperative bleeding. He was treated with three “cardiac” doses of rFVIIa (2.4 mg each), followed by two “hemophiliac” doses (7.2 mg each), which brought his bleeding to 800 mL/h. The patient was subsequently dialyzed and the bleeding stopped completely during hemodialysis.45

A study investigating the use of rFVIIa for reversal of rivaroxaban-induced anticoagulation in a rabbit model found partial improvements in laboratory parameters assessed by aPTT, thromboelastographic clotting time, and the thrombin generation test, but rFVIIa did not reverse rivaroxaban-induced bleeding.86

**Prothrombin complex concentrates.** Outside of VKA reversal, aPCC has a role as a general hemostatic agent in patients with clinically significant bleeding events.67 FEIBA VH (factor VIII inhibitor bypassing activity, vapor heated; Baxter) is an aPCC that contains vitamin K–dependent coagulation factors II, IX, X, and protein C in nonactivated forms and factor VII in the activated form.67

PCCs, both activated and nonactivated, have been suggested to reverse the anticoagulant effects of TSOACs; however, efficacy data for use of some PCCs in this setting are limited and in some cases conflicting. In *in vitro* studies, aPCC (FEIBA) reduced bleeding times in dabigatran-treated rats and PCC inhibited dabigatran-associated intracerebral hematoma expansion in a murine ICH model.45,60 However, PCC (Cofact, Sanquin; fixed dose 50 IU/kg PCC) did not normalize coagulation tests (aPTT, ETP lag time, and TT) in healthy subjects taking dabigatran (150 mg twice a day), even though this treatment did immediately reverse the effects of rivaroxaban (20 mg twice a day) as measured by PT and ETP assays.35

Similar to rFVIIa, PCC partially improved laboratory parameters (aPTT, thromboelastographic clotting time, and the thrombin generation test) in a rabbit model of rivaroxaban-induced bleeding, but did not reverse rivaroxaban-induced bleeding.45 A recent study of healthy volunteers exposed to single doses of rivaroxaban 20 mg and dabigatran 150 mg reported equivocal results for the *ex vivo* effects of PCC, rFVIIa, and FEIBA two hours after TSOAC administration.67 For rivaroxaban, PCC corrected quantitative bleeding parameters (endogenous thrombin potential and maximum concentration of thrombin) and rFVIIa modified kinetic parameters (lag time and time to maximum thrombin concentration), whereas FEIBA corrected all parameters.67 Dabigatran-associated kinetic bleeding parameters were only partially corrected by PCC, rFVIIa, and FEIBA. Lower doses of FEIBA (a quarter to half the usual dose) were found to have the potential to reverse the anticoagulant effects of rivaroxaban and dabigatran.67 A recent open-label study of rivaroxaban 20 mg administered for four days to healthy adults demonstrated that four-factor PCC has a greater effect on reducing the mean PT than three-factor PCC, while three-factor PCC had a greater effect on reversing rivaroxaban-induced changes in endogenous thrombin potential.68 A study of aPCCs using a fibrin network permeability model demonstrated limited reversal of the anticoagulant effects of apixaban.69

An *in vitro* study by Escolar and colleagues used blood from healthy donors to assess PCC (50 IU/kg), aPCC (75 IU/kg), and rFVIIa (270 µg/kg) in reversing the anticoagulant effects of apixaban (200 ng/mL).70 The results showed apixaban administration prolonged clotting time and reduced maximal clot firmness in transmission electron microscope studies using tissue factor as activator;70 Alterations in these parameters by the different reversal agents were variable; the efficacy of rFVIIa was greater than or equal to aPCC, which had greater efficacy than PCC.70

**Emerging Specific Antidotes**

**Monoclonal antibody against dabigatran.** The Fab fragment of a monoclonal antibody with high affinity for dabigatran, aDabi-Fab, is under investigation as a dabigatran antidote. This antibody binds dabigatran with an affinity that is approximately 350 times stronger than the binding of dabigatran to thrombin. This binding correlated with complete inhibition of dabigatran anticoagulant activity *in vitro* (IC₅₀ of 2–4 nM) as measured by the TT assay, as well as reversal of the coagulant effect of dabigatran in rats.71 This monoclonal antibody is under further development.72

**Andexanet alfa.** This modified inactive FXa molecule is under investigation as an antidote for both direct and indirect FXa inhibitors.73 Two phase 2 clinical studies have recently investigated the effect of andexanet alfa in healthy subjects receiving either apixaban 5 mg twice a day or rivaroxaban 20 mg once a day. In subjects receiving apixaban, anti-FXa activity was reduced by 65%, 80%, and 93% within two minutes following intravenous administration of 90 mg, 210 mg, or 420 mg of andexanet alfa, respectively.74 Additionally, a 420 mg-bolus plus a continuous infusion regimen of andexanet alfa for either 45 minutes (180 mg) or two hours (480 mg) showed that mean anti-FXa activity and unbound apixaban decreased by greater than 90% within two minutes of administration of andexanet alfa and that this level of reversal was sustained throughout the infusion period.75 In subjects receiving rivaroxaban, anti-FXa activity decreased by 20% and 53% immediately after administration of andexanet alfa 210 mg and 420 mg, respectively, and rivaroxaban-induced inhibition of thrombin generation and prolongation of both prothrombin time and activated clotting time were partially reversed in a dose-dependent manner.76 These results indicate a rapid sustained dose-related reversal of the anticoagulant activity of apixaban and rivaroxaban, with no serious adverse events. Two randomized, double-blind, placebo-controlled, phase 3 trials currently in progress are investigating the ability of andexanet alfa, as a bolus alone and bolus plus continuous infusion, to reverse the anticoagulant effects of apixaban (NCT02207725) and rivaroxaban (NCT02220725) in healthy subjects ages 50 to 75 years. The initial results from these trials were expected in November 2014.77,78 Further studies in this series will aim to demonstrate the efficacy and safety of andexanet alfa for the reversal of the anticoagulant effects of betrixaban and edoxaban.
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**PER997.** This synthetic small molecule binds directly to the anticoagulant in order to have a reversal effect. It has been shown to reverse the anticoagulant effects of edoxaban, apixaban, dabigatran, rivaroxaban, low-molecular-weight heparin, fondaparinux, and unfractionated heparin *in vitro* and/or in preclinical models.79 An *in vivo* study showed that PER997 decreased bleeding by more than 90% in rats treated with rivaroxaban, dabigatran, and apixaban, reducing bleeding to within the normal range for rats that had not undergone anticoagulation.80 Clinical trials commenced in 2013.

**RECOMMENDATIONS FOR REVERSAL STRATEGIES**

When considering anticoagulant reversal, each patient’s risk of thrombosis and bleeding should be reviewed because details of the medical history and presentation may affect treatment choices. Considerations should include the patient’s clinical status, age, renal function, and laboratory parameters, among others. In some clinical situations, given the short half-lives of the TSOACs, watchful waiting may be appropriate, while in circumstances of higher risk or greater urgency, administration of reversal agents must be considered.

The best reversal strategies vary between anticoagulants, and the data to support each are limited. Vitamin K, FFP, PCC, or aPCC should be used for reversal of warfarin. For the TSOACs, the majority of data come from animal studies. Dialysis and aPCC (FEIBA)—but not PCC (Cofact)—have been shown to be effective in reversing the anticoagulant effect of dabigatran.80,85,60 If dialysis is utilized, the clinician must be mindful of the risk of rebound in plasma dabigatran levels after discontinuation.81 Nevertheless, dialysis of dabigatran is proven, and is preferred over administration of activated charcoal as a removal strategy for this agent. Conflicting results have been published for the reversal of dabigatran using rFVIIa.43,45,60 PCC (Cofact) and aPCC (FEIBA) have been shown to be effective in reversing the anticoagulant effect of rivaroxaban.57,67 Activated charcoal may also be considered for rivaroxaban reversal; however, rFVIIa should not be used.9,11,64 Dialysis is not appropriate for apixaban or rivaroxaban removal because of the high degree of protein binding by these agents.9,11 For reversing the anticoagulant effect of apixaban, rFVIIa, aPCC, and PCC have demonstrated effectiveness, whereas activated charcoal may be useful in the management of apixaban overdose or accidental ingestion.14,70 Andexanet alfa and PER977 (when available) may prove useful for the reversal of various anticoagulants in the future.81

**CONCLUSION**

Clinical decision-making related to anticoagulation requires careful consideration of the risk of bleeding and the risk of stroke or thromboembolism in order to find a balance between efficacy and bleeding risk. Thus, one of the main concerns for clinicians when using TSOACs is understanding when it is safe to proceed with surgical interventions. In the case of nonemergent surgery, the clinician needs to be able to monitor the anticoagulant effect of TSOACs and assess when functional coagulation has been restored. Strategies to monitor the anticoagulant effects of TSOACs are limited at present. In contrast to warfarin, however, the relatively short half-lives of TSOACs cause their anticoagulant effects to diminish rapidly after treatment is discontinued. In the case of emergent surgery, the need to be able to quickly reverse the anticoagulant effect of TSOACs is an ongoing problem. Although supporting evidence is limited and some results have been conflicting, we believe the strategies recommended above represent reasonable approaches to reversing the effects of TSOACs. It is important to note that even within a class of anticoagulant drugs, compounds respond differently to the various reversal agents; therefore, recommendations for one agent should not be extrapolated to another, even if they are from the same therapeutic class. New reversal agents are being explored, including a mouse monoclonal antibody to dabigatran; andexanet alfa, a potential universal FXa inhibitor reversal agent; and PER977, which may be effective for the reversal of FXa inhibitors and direct thrombin inhibitors.

**ACKNOWLEDGMENTS**

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